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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/938,878	08/24/2001	Nila Patil	HO-P02199US2	2515

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PERLEGEN SCIENCES, INC.
LEGAL DEPARTMENT
2021 STIERLIN COURT
MOUNTAIN VIEW, CA 94043

EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 08/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/938,878	PATIL ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *July 28, 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-29,31 and 36-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-29, 31, 36-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 24, 29, 31, 38-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zonana et al (U.S. Patent 6,355,782) in view of Dong et al (U.S. Patent 6,361,947).

Zonana teaches a method of analyzing a subset of nucleic acids (see abstract) comprising:

(a) providing a driver population of nucleic acid and a tester population of nucleic acids (See column 22, lines 64-65 for driver and column 22, line 66 to column 23, line 8 for tester),

(b) denaturing said population of tester and driver nucleic acids (see column 23, lines 9-16),

(c) annealing the driver and tester populations to produce a single stranded subset of nucleic acids and a double stranded subset of nucleic acids (see column 23, lines 15-18),

(d) immobilizing the driver population of nucleic acids by use of a biotin-streptavidin interaction to produce an unimmobilized single stranded tester subset of nucleic acids, an immobilized double stranded tester-driver subset of nucleic acids and an immobilized single stranded driver subset of nucleic acids (see column 23, lines 18-19),

(e) separating the unimmobilized single stranded tester subset of the nucleic acids from the single and double stranded driver subset of the nucleic acids (see column 23, lines 20-21),

(f) dissociating the immobilized double stranded tester-driver subset of nucleic acids to produce a subset of complementary tester nucleic acids and a subset of immobilized complementary driver nucleic acids (see column 23, lines 22-23)

(g) separating the subset of complementary tester nucleic acids from the subset of immobilized complementary driver nucleic acids (see column 23, lines 22-23).

Zonana amplifies the driver from genomic DNA (see column 22, where Bacs which contained fragments that comprise "genomic" DNA are used).

Zonana does not teach the steps of:

(h) hybridizing the unimmobilized single stranded tester nucleic acids to probes on a nucleic acid probe array (see page 1890, column 2, subheading "colony hybridization" and figure 3) and

(i) determining which of the probes on the array hybridizes to the single stranded tester subset of the population thereby analyzing the single stranded subset of the population of nucleic acid fragments (see page 1890, column 2, subheading "colony hybridization and figure 3).

Dong teaches the steps of

(h) hybridizing the unimmobilized single stranded tester nucleic acids to probes on a nucleic acid probe array (see column 5, lines 57-60 and column 31, claim 1)) where Dong further teaches that "In a preferred embodiment the isolated sequences are then exposed to an array which may or may not have been specifically designed and manufactured to interrogate the isolated sequences. Design of both the complexity management steps and the arrays may be aided by the computer modeling techniques which are also described in the present invention (see column 5, lines 58-61)" and

(i) determining which of the probes on the array hybridizes to the single stranded tester subset of the population thereby analyzing the single stranded subset of the population of nucleic acid fragments (see column 5, lines 57-60 and column 31, claim 1).

With regard to claim 29, Zonana teaches the use of PCR products as driver (see column 22, lines 64-65).

With regard to claims 38 and 39, Zonana teaches the driver has a biotin tag and binds to streptavidin magnetic beads (see column 23, lines 18-19).

With regard to claim 40, Zonana teaches separating the subset of complementary tester nucleic acids from the subset of immobilized complementary driver nucleic acids using the biotin streptavidin interaction (see column 23, lines 22-23),

With regard to claim 31, Dong teaches restriction digestion of the sample which will result in more than ten noncontiguous regions of driver (see columns 6-8).

Dong, in figure 4, expressly shows drivers which are from noncontiguous regions and in column 7 discusses other modes to form drivers using PCR which are drawn to noncontiguous regions. With regard to the "previously characterized polymorphic sites", this element is also taught by Dong (see figure 3, for example). Dong expressly uses total genomic DNA (see column 15, line 37, where "total genomic DNA" is used).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Zonana with the detection method of Dong since Zonana wants to selected cDNA and since Dong states "In a preferred embodiment the isolated sequences are then exposed to an array which may or may not have been specifically designed and manufactured to interrogate the isolated sequences. (see column 5, lines 57-60)." An ordinary practitioner would have recognized that both Zonana and Dong were operating to reduce the complexity of their DNA sample and were selecting for subsets of the total sample. In this context, an ordinary practitioner would have been motivated by Dong to use an array in the place of the more cumbersome cloning methods used by Zonana for further analysis

since Dong expressly teaches that array detection is a preferred method of analysis of the isolated subsets.

4. Claims 25-28, 36-37 and 41-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zonana et al (U.S. Patent 6,355,782) in view of Dong et al (U.S. Patent 6,361,947) as applied to claims 24, 29 and 38-40 and further in view of Wigler et al (U.S. Patent 5,501,964).

Zonana et al (U.S. Patent 6,355,782) in view of Dong et al (U.S. Patent 6,361,947) teach the limitations of claims 24, 29 and 38-40 as discussed above. Zonana et al (U.S. Patent 6,355,782) in view of Dong et al (U.S. Patent 6,361,947) do not teach screening fragments from human individuals or the use of two different human individuals or comparison of different species or the DNA or mRNA sources used.

Wigler teaches comparison of DNA from two sources in order to determine the relationship between the sources (See column 3, lines 11-14) including comparisons between different individuals (see column 8, lines 40-48) as well as comparisons between different species (see column 21, example 7), which address the limitations of claims 27-28, 42, 49-50, 56-57.

With regard to claims 25-26, 46-48, 54-55, Wigler teaches that the sources can be cDNA, genomic DNA, restriction fragments of DNA or libraries (see column 2, lines 42-50).

With regard to claims 31, 52, 53, the cDNA drivers would necessarily be derived from noncontiguous regions of a genome of a species. Wigler also teaches comparison of PCR amplified DNA (see column 4, lines 28-37). Wigler expressly recognizes that

any animal can be the source of the DNA, including mammals and non-mammals, as well as higher eukaryotes and humans.(see column 3, lines 62-67).

With regard to claims 41, 45, 51, 58, Zonana teaches the use of PCR products as driver prior to step (a) (see column 22, lines 64-65) and Wigler teaches the use of genomic DNA (see column 2, lines 42-50).

With regard to claim 43, Zonana teaches the use of PCR and no specific length difference exists for "long range PCR" in the specification and so this term does not distinguish from ordinary PCR.

With regard to claim 44, 51, Zonana teaches PCR to amplify tester nucleic acid (see column 23, lines 1-15).

With regard to claims 60-61, Zonana teaches the driver has a biotin tag and binds to streptavidin magnetic beads (see column 23, lines 18-19).

With regard to claim 62, Zonana teaches immobilizing the driver population of nucleic acids by use of a biotin-streptavidin interaction to produce an unimmobilized single stranded tester subset of nucleic acids, an immobilized double stranded tester-driver subset of nucleic acids and an immobilized single stranded driver subset of nucleic acids (see column 23, lines 18-19),

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Zonana et al (U.S. Patent 6,355,782) in view of Dong et al (U.S. Patent 6,361,947) to utilize the different comparisons and DNA sources for comparison taught by Wigler since Wigler states

> "Comparative genomic DNA analysis holds promise for the discovery of sequences which may provide for information

> concerning polymorphisms, infectious DNA based agents, lesions associated with disease, such as cancer, inherited dominant and recessive traits, and the like. By being able to detect particular DNA sequences which have a function or affect a function of cells, one can monitor pedigrees, so that in breeding animals one can follow the inheritance of particular sequences associated with desirable traits. In humans, there is substantial interest in forensic medicine, diagnostics and genotyping, and determining relationships between various individuals. There is, therefore, substantial interest in providing techniques which allow for the detection of common sequences between sources and sequences which differ between sources. (Column 1, lines 23-37)."

An ordinary practitioner would have been motivated to apply the tester driver method of Zonana et al (U.S. Patent 6,355,782) in view of Dong et al (U.S. Patent 6,361,947) on comparisons between individuals and between species in order to identify desirable traits, as expressly suggested by Wigler, as well as identifying relationships between individuals and species as suggested by Wigler. An ordinary practitioner would have been motivated to focus on a comparison of unique sequences as taught by Zonana and Dong in the broad variety of contexts suggested by Wigler.

Further, with regard to the order of the steps of immobilization, annealing and denaturation, as in claim 59, for example, as MPEP 2144.04 notes "selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results". In this case, this is particularly true since the order of the steps would not be expected to impact the results of the method. Whether immobilization was performed prior to the annealing or denaturation steps would not be expected to effect the reaction since the interaction is between the nucleic acids, which are equally available whether immobilized or not.

Response to Arguments

5. Applicant's arguments filed July 28, 2005 have been fully considered but they are not persuasive.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, there is abundant motivation to combine the references of Zonana and Dong since the combination permits interrogation of the sequences isolated by Zonana to determine if these sequences are wildtype or mutant, if these sequences have one haplotype or another haplotype, or if these sequences have the sequence expected for the dI nucleic acid or

not. Thus, an ordinary practitioner would have been motivated by Dong to interrogate the selected products of Zonana for a variety of different analyses, all of the analyses being ones expressly suggested by Zonana.

Applicant then argues that Zonana does not teach the use of drivers that meet the newly added limitation of "two or more noncontiguous regions within a genome". While Zonana does not teach this element, Dong does. Dong, in figure 4, expressly shows drivers which are from noncontiguous regions and in column 7 discusses other modes to form drivers using PCR which are drawn to noncontiguous regions. Therefore, the combination of Dong with Zonana teaches the argued limitation and the rejection remains proper. It is this combination which renders the claim prima facie obvious, not Zonana alone.

With regard to the "previously characterized polymorphic sites", this element is also taught by Dong (see figure 3, for example).

Lastly, Applicant argues that the prior art does not teach the use of "genomic" DNA. This is simply incorrect. All of the nucleic acids are drawn from genomic DNA. Zonana amplifies the driver from genomic DNA (see column 22, where Bacs which contained fragments that comprise "genomic" DNA are used), Dong expressly uses total genomic DNA (see column 15, line 37, where "total genomic DNA" is used) and Wigler also teaches the use of genomic DNA as a starting point (see column 4, lines 37-55, for example). Therefore, the prior art teaches and suggests all of the limitations of the claims and the rejections remain proper.

Conclusion

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1637
8/11/05